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RESEARCH ARTICLE

The relationship between polymorphisms of genes regulating DNA repair or cell division and the toxicity of platinum and vinorelbine chemotherapy in advanced NSCLC patients

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Abstract

Introduction Platinum-based chemotherapy and 3rd generation drugs is still the main treatment option for advanced non-small cell lung cancer (NSCLC) patients without activating *EGFR* mutations or *ALK* rearrangements. However, the side effects associated with cytostatics are well known. Changes in the genes (e.g. single nucleotide polymorphisms, SNPs) encoding proteins regulating DNA repair or cell division could potentially influence on both the susceptibility of cancer cells to chemotherapy, and the occurrence of toxicities.

Materials and methods In presented study, the relationship between the fourteen SNPs in nine DNA repair and cell division regulating genes: *ERCC1, XPD*, *XPA*, *XPC*, *XRCC1*, *XPG*, *RRM1*, *BRCA1*, *STMN1* and the toxicity of first-line chemotherapy in NSCLC patients were investigated. SNPs were determined by SNaPshot PCR® in DNA isolated from peripheral blood of 55 NSCLC patients treated with platinum compound and vinorelbine. The toxicity of therapy was evaluated according to the Common Toxicity Criteria (CTC) Version 4.03.

Results The odds ratio (OR) of severe haematological toxicity was significantly lower in carriers of the T allele of *XRCC1* gene (1196A > G, OR = 0.22, 95 % CI: 0.06–0.82, $p = 0.018$) and higher in the carriers of the T allele (2704C > A) of *XPC* gene (OR: 7.50, 95 % CI: 0.89–63.17, $p = 0.036$) compared to the remaining patients. Risk of severe hepatotoxicity was significantly lower in carriers of the C allele of *STMN1* (−2166T > C, OR = 0.09, 95 % CI: 0.01–1.12, $p = 0.025$) than in patients with T allele of this gene. In carriers of G allele (2251A > C, OR: 0.24, 95 % CI: 0.07–0.81, $p = 0.017$) and T (934G > A, OR: 0.26, 95 % CI: 0.07–0.90, $p = 0.029$) of *XPD* gene, risk of severe nephrotoxicity was significantly lower than in other patients.

Conclusions Selected SNPs of genes encoding DNA repair enzymes and cell division regulation proteins could be useful biomarkers for prediction of platinum and vinorelbine-based chemotherapy toxicity in patients with advanced NSCLC.

Keywords SNPs · DNA repair · STMN1 · Toxicity · Chemotherapy · Non-small cell lung cancer

Introduction

Lung cancer (85 % of cases are represented by NSCLC) is still the leading cause of death from malignancies in the world [1, 2]. This is despite the dynamic development of early diagnostic methods, molecularly targeted therapies and immunotherapy of cancer. The majority of NSCLC patients are diagnosed at an advanced stage of disease, which limits the therapeutic options. Therefore, systemic

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therapy, based on chemo- or chemoradiotherapy, is the most important method of treatment of NSCLC patients. However, chemotherapy is characterized by moderate efficacy and significant toxicity. Molecularly targeted drugs (tyrosine kinases inhibitors of EGFR, e.g. erlotinib, gefitinib, afatinib or ALK, e.g. crizotinib, ceritinib) are more effective, however, only in patients with specific molecular abnormalities (activating mutations in the *EGFR* gene or *ALK* gene rearrangements) [3, 4]. In the first line of NSCLC treatment, a combination of platinum compound (cisplatin or carboplatin) and third generation drug (gemcitabine, vinorelbine, pemetrexed, docetaxel or paclitaxel) is used [5]. The various cytostatic drugs have different mechanisms of action: direct or indirect damage of DNA, interfering of DNA replication or damage of the mitotic spindle. Due to the cell structure destruction and blocking life processes, cytostatics affect both normal and cancerous cells and cause numerous side effects.

STMN1 (oncoprotein-18) is a protein related to microtubule dynamics and regulation of the cell cycle [11, 12]. Expression of STMN1 and the presence of different tubular protein isoforms (e.g. TUBB3) have the greatest impact on the possibility of cell proliferation. In available literature, there are no data about influence of *STMN1* gene polymorphisms (including $-2166T > C$, rs182455) on the chemotherapy toxicity in lung cancer patients. However, on the basis of knowledge about the correlation between the expression of *STMN1* and efficacy of therapies based on taxanes or *vinca* alkaloids, it can be assumed that the *STMN1* gene polymorphisms could be considered as a predictive factor in lung cancer patients [6, 7].

DNA repair capacity plays important roles in carcinogenesis, response to cancer treatment, and toxicity of chemotherapy. Polymorphisms (e.g. single nucleotide polymorphisms, SNPs) of the genes encoding DNA repair enzymes associated with the changes of DNA repair effectiveness may influence on both susceptibility of tumour cells to chemotherapy as well as the occurrence of the related toxicity. The above hypothesis is confirmed by some of the recently published researches. Several SNPs of genes encoding enzymes involved in different mechanisms of DNA repair, including nucleotide excision repair (NER): *ERCC1*, *XPA*, *XPC*, *XPG*, *XPD*, *MMS18L*, base excision repair (BER): *XRCC1*, *BRCA1*, mismatch repair (MMR): *RECQ1* as well as nucleotide synthesis: *RRM1*, *TS*, *MTHFR*, have been investigated in patients with advanced NSCLC [8–13]. These SNPs, associated with lung cancer risk and response to treatment, may be also the predictors for toxicity of chemotherapy [14–17]. Unfortunately, only few clinical trials, that assess the association between SNPs of DNA repair genes and the toxicity of various chemotherapy regimens, are available in literature. In most cases, these are retrospective studies and the obtained results are often inconsistent, which further complicates their unequivocal evaluation.

The aim of this study was to evaluate the relationship between the 14 SNPs located in 9 genes regulating DNA repair or cell division (*ERCC1*: 19007C > T, rs11615; 8092C > A, rs3212986; *XPD*: 2251A > C, rs13181; 934G > A, rs1799793; *XPA*: 4A > G, rs1800975; *XPC*: 1385C > T, rs2228000; 2704C > A, rs2228001; *XRCC1*: 580C > T, rs1799782; 1196A > G, rs25487; *XPG*: 3310G > C, rs17655; *RRM1*: −37C > A, rs12806698; −524C > T, rs11030918; *BRCA1*: 181T > A/C/G, rs28897672; *STMN1*: −2166T > C, rs182455) and the toxicity of first-line chemotherapy based on platinum and vinorelbine in advanced NSCLC patients.

Materials and methods

The study group

This retrospective study included 55 Caucasian patients with inoperable, locally advanced or advanced NSCLC (IIIB and IV) treated in 2010–2013 at the Department of Pneumonology, Oncology and Allergology, Medical University of Lublin. The project was approved by the Committee of Ethics and Research at the Medical University of Lublin (no. consent: KE-0254/142/2010). The condition of participation in the study was patients' written consent to the use of clinical data and material in the form of peripheral blood. NSCLC diagnoses were based on pathomorphological examination. Standard regimen and dosing of chemotherapy were used in the I line of chemotherapy (recommended by Polish Society of Clinical Oncology consistent with the guidelines of the European Society for Medical Oncology, ESMO and the National Comprehensive Cancer Network, NCCN). All patients received platinum compounds and vinorelbine.

Stage of a disease was evaluated according to TNM classification (VII edition by the Union for International Cancer Control, UICC). The median number of cycles of I-line chemotherapy was 4 (4–6). Based on an interview and the available medical documentation detailed demographic and clinical data (gender, age, smoking status, type of NSCLC, stage of disease, weight loss and performance status, type and number of cycles of chemotherapy, side effects) were collected. Response to treatment was evaluated by RECIST Version 1.1 (Response Evaluation Criteria in Solid Tumours). Adverse events were assessed after 2nd and 4th cycle, based on CTC Version 4.03 (Common Toxicity Criteria). Haemoglobin level as well as blood red and white cells number and percentage were assessed before any medication of anaemia or bone marrow damage (e.g. red blood cells transfusion or granulocyte colony-

stimulating factor (G-CSF) administration). The later obtained data were discarded. The degree of renal failure was determined on the basis of serum creatinine level and glomerular filtration rate (eGFR). Serum bilirubin and transaminases (AST, ALT) levels were used for estimation of liver failure. The factors describing the toxicity were observed for 4 weeks after the chemotherapy termination.

The applied methods

For the isolation of DNA from peripheral blood leukocytes, DNA Blood Mini Kit (Qiagen, Canada) was used. The quantity and quality of extracted DNA were performed using a spectrophotometer BioPhotometer plus cuvette equipped with filters UV/IS (Eppendorf, Germany). Analysis of SNPs of studied genes was carried out by the minisequencing technique (SNaPshot® PCR) and ABI PRISM SNaPshot® Multiplex (Life Technologies, USA).

Genotyping results of analysed genes were retrospectively related to demographic and clinical characteristics and the occurrence of chemotherapy toxicity (haematological and non-haematological). Statistical analysis of the results was performed using the computer software MedCalc Version 10 (MedCalc Software, Belgium). $p < 0.05$ was considered statistically significant. The Hardy–Weinberg (HW) equilibrium and the Chi-Square (χ^2) test were used for assessment of allele and genotypes frequencies as well as for evaluation of relationship demographic and clinical factors with the distribution of polymorphic variants of the studied genes.

Results

Clinical characteristics

Baseline characteristics of study population are presented in Table 1. None of patients has received radical radiotherapy; however, 14.5 % of patients were radiated as palliative treatment to reduce symptoms caused by airway obstruction or by distant metastasis. There was no complete remission (CR) as a result of first-line chemotherapy. Control of the disease was recorded in 70.9 % of patients, of which the PR and SD occurred in 20 % and 50.9 % of patients. PD was observed in 29.1 % of patients. The median progression-free survival (PFS) and follow-up time were 5 ± 3 and 9 ± 3 months, respectively.

SNPs analysis

The genotypes distribution of investigated genes is shown in Table 2. Only AA homozygotes (100 %) of *BRCA1* gene were found in the study group. Accordingly, the polymorphism of this gene was not included in the statistical analysis. Genotype frequencies were in accordance with Hardy–Weinberg equilibrium model and consistent with previous studies (if they were available).

Chemotherapy toxicity

Patients who received at least two cycles of chemotherapy were evaluated for possible side effects. Severe toxicity (grade 2–4) was detected in 17 patients (30.9 %) after second and in 29 patients (52.7 %) after fourth cycle of chemotherapy, including all assessed types of toxicity. Haematologic toxicity was most common adverse events. Grade 2–4 haematologic toxicity after second cycle of chemotherapy appeared in 4 patients (7.3 %), whereas grade 2–4 toxicity after fourth cycle of chemotherapy—in 14 patients (25.5 %). Lack of haematological toxicity was recorded in 15 patients (27.3 %) after second cycle of chemotherapy and in 4 patients (7.3 %) after forth cycle of chemotherapy. Severe hepatotoxicity was not found in any patient after 2nd cycle of chemotherapy, but its occurrence was observed in 3 patients (5.5 %) after 4th cycle of chemotherapy. Hepatotoxicity was not detected in 47 patients (85.5 %) after 2nd cycle of chemotherapy and in 43 patients (78.2 %) after 4th cycle of chemotherapy. Grade 2–4 hepatotoxicity was recorded in 15 patients (27.3 %) after 2nd cycle of chemotherapy and 16 patients (29.1 %) after 4th cycle of chemotherapy. No nephrotoxicity was observed in 18 (32.7 %) and 16 (29.1 %) patients, retrospectively. Severe nephrotoxicity after 2nd cycle of chemotherapy was observed significantly more frequently in elderly patients (≥64 years) compared to younger patients (<64 years) ($p = 0.001$, $\chi^2 = 14.610$). Other toxicities occurred with similar frequency in groups of patients with different clinical-demographic characteristics (Table 3).

SNPs and chemotherapy toxicity

Association between toxicity after chemotherapy and SNPs in genes encoding proteins regulating DNA repair and mitotic spindle were presented in Supplementary Tables 1S–3S. The odds ratio (OR) of early (after 2nd cycle of chemotherapy) severe haematological toxicity was significantly lower in carriers of G allele of *XPD* gene (934G > A, OR = 0.08, 95 % CI 0.01–0.40, $p = 0.0005$) and *XPA* gene (4A > G, OR = 0.07; 95 % CI 0.01–1.41, $p = 0.018$) than in carriers of A allele of these genes. Risk of early severe nephrotoxicity was significantly lower in carriers of C allele of *XPD* gene (2251A > C, OR = 0.07, 95 % CI 0.02–0.31, $p < 0.0001$) than in patients with A allele of this gene.

The OR of severe haematological toxicity after 4th chemotherapy cycle was significantly lower in carriers of A allele of *XRCC1* gene (1196A > G, OR = 0.22, 95 % CI

Table 1 Characteristics of the study group

Factors	Characteristics
Whole group (*n*)	55
Gender	
Male (*n*; %)	40 (72.7)
Female (*n*; %)	15 (27.3)
Age in years (median ± SD; range 51–77)	64 ± 7
≤64 years (*n*; %)	32 (58.2)
>64 years (*n*; %)	23 (41.8)
Performance Status (PS)	
PS = 0 (*n*; %)	11 (20)
PS = 1 (*n*; %)	44 (80)
Weight loss	
<5 % (*n*; %)	47 (85.5)
≥5 % (*n*; %)	8 (14.5)
Smoking status	
Current Smoker (*n*; %)	29 (52.7)
Ex-smoker (*n*; %)	21 (38.2)
Non-smoker (*n*; %)	5 (9.1)
Disease stage	
IIIB (*n*; %)	36 (65.5)
IV (*n*; %)	19 (34.5)
Pathomorphological diagnosis	
Adenocarcinoma (*n*; %)	11 (20)
Squamous-cell carcinoma (*n*; %)	34 (61.8)
Large-cell carcinoma (*n*; %)	6 (10.9)
Not otherwise specified (NSCLC-NOS) (*n*; %)	4 (7.3)
Prior surgical treatment	
Yes (*n*; %)	6 (10.9)
No (*n*; %)	49 (89.1)
Radiotherapy	
Yes (*n*; %)	8 (14.5)
No (*n*; %)	47 (85.5)
No. of first-line chemotherapy cycles: median (range)	4 (4–6)
Response to chemotherapy	
PR (partial remission) (*n*; %)	11 (20)
SD (stable disease) (*n*; %)	28 (50.9)
PD (progressive disease) (*n*; %)	16 (29.1)
PFS (median ± SD), range 1–12	5 ± 3 months
OS (median ± SD), range 3.5–15	9 ± 3 months

0.06–0.82, $p = 0.018$), however, significantly higher in carriers of A allele of *XPC* gene (2704C > A,OR = 7.50, 95 % CI 0.89–63.17, $p = 0.036$) compared to patients with other alleles of these genes. The OR of severe hepatotoxicity after 4th chemotherapy cycle was significantly lower in carriers of C allele of *STMN1* gene (−2166T > C, OR = 0.09, 95 % CI 0.01–1.12, $p = 0.025$) than in carriers of T allele of this gene. Risk of severe nephrotoxicity after 4th chemotherapy cycle was significantly lower in carriers of C allele (2251A > C, OR = 0.24, 95 % CI 0.07–0.81, $p = 0.017$) and A allele (934G > A, OR = 0.26, 95 % CI 0.07–0.90, $p = 0.029$) of *XPD* gene compared to patients carried A or G allele of this gene. No statistically significant association between the other examined SNPs and chemotherapy toxicities was found.

Discussion

Cytostatic drugs, used currently in chemotherapy of NSCLC, are harmful for both tumour and normal cells. Direct or indirect damage of the genetic material, related to the regulation of cell division, occurs in the rapidly proliferating and active cells. Numerous side effects in bone marrow, kidneys and liver are observed at the site of cytostatics metabolism and after cytostatics exposure. Alkylating agents (platinum compounds: cis- and carboplatin) and inhibitors of mitosis through interaction with tubulin (vinorelbine, docetaxel, paclitaxel) induce myelosuppression, renal and liver failure, hair loss, diarrhoea, nausea and vomiting, peripheral neuropathy, weakness, hearing disorders [18].

Qualification of NSCLC patients to different chemotherapy regimens is based mainly on the performance status of the patient, convenience of the drugs use and the personal experiences of physician. However, currently available chemotherapy regimens are characterized by significant differences in toxicity. It is clear that toxicity profile is not applies equally to all patients and is associated with molecular differences [6, 7, 19–21]. Changes in the structure, function or expression of particular proteins are conditioned by the occurrence of SNPs in coding or non-coding sequences (mainly promoter) of genes [22]. SNPs analysis can be realized in materials that are easy to obtain (e.g. DNA from peripheral blood leukocytes). Consequently, in many studies (unfortunately mainly retrospective), the effects of the individual polymorphic variants of different genes on the effectiveness and toxicity of the chemotherapy regimens were examined. However, most of the major research was carried out on Asian patients. Moreover, the results presented in the literature are often contradictory and inconclusive.

Zhang et al. [8] examined polymorphisms of *ERCC5*, *ERCC6*, *MMS19L*, *CCNH*, *XPC*, *RRM1* genes in 365 Asian patients with locally advanced or advanced NSCLC treated with platinum-based chemotherapy. Authors showed that presence of G allele in codon 811 of *MMS19L* gene was associated with the occurrence of haematological toxicity (leukopenia, thrombocytopenia), hepatotoxicity (icterus) and nephrotoxicity. However, polymorphism C37A (rs 12806698) in *RRM1* gene was associated with higher incidence of vomiting and D1104H (rs17655) in *ERCC5*

Table 2 Distribution of studied genotypes

Lp.	SNP	MAF	AA	AC	CC	Hardy–Weinberg equilibrium	
						p	χ^2
1.	*ERCC1* (8092C > A), *n* (%)	A = 28.4%	3 (5.5)	29 (52.7)	23 (41.8)	0.1104	2.5480
2.	*XPD/ERCC2* (2251A > C), *n*(%)	G = 35.7%	21 (38.1)	30 (54.6)	4 (7.3)	0.1263	2.3372
3.	*XPC* (2704C > A), *n* (%)	G = 35.2%	11 (20)	28 (50.9)	16 (29.1)	0.8432	0.0391
4.	*RRM1* (−37C > A), *n* (%)	A = 30.9%	2 (3.6)	29 (52.8)	24 (43.6)	0.0582	3.5879
			AA	AG	GG		
5.	*XPA* (−4A > G), *n* (%)	T = 35.6%	24 (43.6)	26 (47.3)	5 (9.1)	0.5853	0.2977
6.	*XPD/ERCC2* (934G > A), *n* (%)	T = 38.3%	9 (16.4)	30 (54.6)	16 (29)	0.4194	0.6519
7.	*XRCC1* (1196A > G), *n* (%)	T = 33.3%	4 (7.3)	25 (45.4)	26 (47.3)	0.5419	0.3721
			CC	CT	TT		
8.	*XPC* (1385C > T), *n* (%)	A = 19.5%	39 (70.9)	14 (25.5)	2 (3.6)	0.6034	0.2699
9.	*ERCC1* (19007C > T), *n* (%)	A = 40.3%	7 (12.7)	30 (54.6)	18 (32.7)	0.3119	1.0227
10.	*XRCC1* (580C > T), *n*(%)	A = 6%	50 (90.9)	5 (9.1)	0	0.7240	0.1247
11.	*RRM1* (−524C > T), *n* (%)	C = 34.1%	6 (10.9)	27 (49.1)	22 (40)	0.5903	0.2898
12.	*STMN1* (−2166T > C), *n* (%)	A = 35.8%	18 (32.7)	27 (49.1)	10 (18.2)	0.9820	0.0005
			CC	CG	GG		
13.	*XPG/ERCC5* (3310C > G), *n* (%)	C = 16.6%	1 (1.8)	17 (30.9)	37 (67.3)	0.5453	0.3658

MAF minor allele frequency (global, from SNPs data base available on pubmed website)

gene—with susceptibility to infections. Lambet al. [23] showed that SNPs in *ERCC4* and *XPC* genes were significantly related to risk of neutropenia in 90 Caucasian male patients treated with the combination of carboplatin and paclitaxel. Wu et al. [11] noted that the incidence of severe haematologic toxicity (especially leucopoenia) was significantly higher in the AA genotype carriers (396A > C, rs238406) of *XPD* gene in 209 Asian NSCLC patients received chemotherapy based on platinum compounds. Two other SNPs (934G > A, rs1799793; 2133C > T, rs1052555) of this gene had no effect on the occurrence of chemotherapy toxicity. Suk et al. [10] showed a relationship between the presence of A allele of *ERCC1* gene (8092C > A, rs3212986) and an increased risk of serious gastrointestinal tract toxicity in 214 Caucasian patients with inoperable or advanced NSCLC treated with platinum-based chemotherapy.

Many authors have failed to find any association between the occurrence of DNA repair genes polymorphisms and risk of chemotherapy toxicity. An example is a study of Li et al. conducted in 115 Asian and locally advanced or metastatic NSCLC patients treated with platinum-based chemotherapy. SNPs 2251A > C (rs13181) of *XPD* gene and 1196 > G (rs25487) of *XRCC1* gene were not significantly associated with haematological and gastrointestinal toxicity as well as hepatotoxicity [24]. Sullivan et al. [25] examined 116 Caucasian NSCLC Caucasian patients treated platinum-based chemotherapy. Authors analysed 17 SNPs in 8 genes (*ERCC1*: rs11615, rs3212948, rs3212986, *ERCC2/XPD*: rs1799793, rs13181; *ERCC3/XPB*: rs4150454, rs4150402, rs3738948; *ERCC4/XPF*: rs1799801; *ERCC5/XPG*: rs1047768, rs17655; *XPA*: rs1800975; *XRCC1*: rs25487, rs25489, rs1799782, rs3213239, *XRCC2*, rs3218536) related to DNA repair. They did not find any association between these polymorphisms and haematological and gastrointestinal toxicities.

In the present study, we showed that the risk of early, severe haematological toxicity or nephrotoxicity significantly depends on polymorphisms in *XPD* and XPA gene in NSCLC patients treated with platinum compounds and vinorelbine. In contrast, a higher risk of severe haematological toxicity after 4th chemotherapy cycle correlated with specific genotypes of *XPC*, *XRCC1* and *XPD* genes.

At present, no data are available about the role of polymorphisms of *STMN1* gene (including rs 182455) in sensitivity to chemotherapy and risk of chemotherapy toxicity in NSCLC patients. In studies conducted in breast and ovarian cancer cell lines, Alla et al. and Balachandran et al. [26, 27] demonstrated that the increased expression of STMN1 reduced microtubule polymerization with significantly reduction of paclitaxel binding. The increased expression of STMN1 leads to increased vinblastine's annealing, indicating that the disorders in expression of STMN1 may be associated not only with resistance to the taxanes but also to *vinca* alkaloids. Meng et al. [7] showed that a low level of STMN1 expression is a favourable predictor of response to neoadjuvant chemotherapy based

Table 3 The impact of demographic and clinical factors on the occurrence of adverse events

Factor	After 2nd chemotherapy cycle									After 4th chemotherapy cycle								
	Haematological toxicity			Hepatotoxicity			Nephrotoxicity			Haematological toxicity			Hepatotoxicity			Nephrotoxicity		
	None or mild	Severe	P χ^2	None or mild	Severe	P χ^2	None or mild	Severe	P χ^2	None or mild	Severe	P χ^2	None or mild	Severe	P χ^2	None or mild	Severe	P χ^2
All group, *n* (%)	51 (92.7)	4 (7.3)	–	55	0	–	40 (72.7)	15 (27.3)	–	41 (74.5)	14 (25.5)	–	52 (94.5)	3 (5.5)	–	39 (70.9)	16 (29.1)	–
Sex																		
Male, *n* (%)	38 (69.2)	2 (3.6)	0.227	40 (72.7)	0	–	29 (52.7)	11 (20)	0.951	30 (54.5)	10 (18.2)	0.899	37 (67.2)	3 (5.5)	0.671	29 (52.7)	11 (20)	0.928
Female, *n* (%)	13 (23.6)	2 (3.6)	0.633	15 (27.3)	0		11 (20)	4 (7.3)	0.004	11 (20)	4 (7.3)	0.016	15 (27.3)	0	0.180	10 (18.2)	5 (9.1)	0.008
Age (years)																		
<64, *n* (%)	31 (56.3)	1 (1.8)	0.384	32 (58.2)	0	–	30 (54.6)	2 (3.6)	0.001	27 (49)	5 (9.1)	0.097	30 (54.6)	2 (3.6)	0.759	26 (47.3)	6 (10.9)	0.091
≥64, *n* (%)	20 (36.4)	3 (5.5)	0.758	23 (41.8)	0		10 (18.2)	13 (23.6)	14.61	14 (25.5)	9 (16.4)	2.756	22 (40)	1 (1.8)	0.094	13 (23.6)	10 (18.2)	2.859
Smoking status																		
Smokers, *n* (%)	28 (50.9)	1 (1.8)	0.134	29 (52.7)	0	–	22 (40)	7 (12.7)	0.909	23 (41.8)	6 (10.9)	0.904	27 (49)	2 (3.6)	0.852	20 (36.4)	9 (16.4)	0.957
Ex-smokers, *n* (%)	20 (36.4)	1 (1.8)	4.020	21 (38.2)	0		14 (25.5)	7 (12.7)	0.191	15 (27.3)	6 (10.9)	0.202	20 (36.4)	1 (1.8)	0.321	16 (29)	5 (9.1)	0.088
Non-smokers, *n* (%)	3 (5.5)	2 (3.6)		5 (9.1)	0		4 (7.3)	1 (1.8)		3 (5.5)	2 (3.6)		5 (9.1)	0		3 (5.5)	2 (3.6)	
Histopathological diagnosis																		
Adenocarcinoma, *n* (%)	10 (18.2)	1 (1.8)	0.961	11 (20)	0	–	8 (14.5)	3 (5.5)	0.604	9 (16.4)	2 (3.6)	0.950	11 (20)	0	0.864	7 (12.7)	4 (7.3)	0.686
			0.294						1.852			0.353			0.737			1.483
Squamous-cell carcinoma, *n* (%)	32 (58.6)	2 (3.6)		34 (62.2)	0		23 (41.8)	11 (20)		25 (45.7)	9 (16.4)		31 (56.3)	3 (5.5)		23 (41.8)	11 (20)	
Large-cell carcinoma, *n* (%)	6 (10.9)	0		6 (10.9)	0		6 (10.9)	0		5 (9.1)	1 (1.8)		6 (10.9)	0		6 (10.9)	0	
NSCLC-NOS, *n* (%)	3 (5.5)	1 (1.8)		4 (7.3)	0		4 (7.3)	0		2 (3.6)	2 (3.6)		4 (7.3)	0		3 (5.5)	1 (1.8)	
Stage of disease																		
IIIB, *n* (%)	33 (60.1)	3 (5.5)	0.677	36 (65.5)	0	–	25 (45.7)	11 (19.8)	0.664	25 (45.7)	11 (20)	0.384	36 (65.8)	0	0.068	24 (43.6)	12 (21.8)	0.521
IV, *n* (%)	18 (32.7)	1 (1.8)	0.174	19 (34.5)	0		15 (27.3)	4 (7.2)	0.188	16 (28.8)	3 (5.5)	0.757	16 (28.8)	3 (5.4)	3.340	15 (27.3)	4 (7.3)	0.411
Performance status																		
PS = 0, *n* (%)	11 (20)	0	0.152	11 (20)	0	–	9 (16.4)	2 (3.6)	0.705	11 (20)	0	0.075	10 (18.2)	1 (1.8)	0.882	9 (16.4)	2 (3.6)	0.603
PS = 1, *n* (%)	40 (73)	4 (7.3)	0.697	44 (80.2)	0		31 (56.4)	13 (23.6)	0.143	30 (54.5)	14 (25.5)	3.168	42 (76.4)	2 (3.6)	0.022	30 (54.5)	14 (25.5)	0.270

on docetaxel in 54 women with advanced breast cancer. Both *vinca* alkaloids and taxanes affect not only tumour cells. Therefore, disturbances in the expression of the *STMN1* gene can influence on side effects of chemotherapy. In the present study, for the first time, the relationship of SNP −2166T > C of *STMN1* gene with hepatotoxicity was described in NSCLC patients treated with platinum compounds and vinorelbine.

Undoubtedly, the limitations of this study are retrospective nature and small examined group. While, the advantages of the present study are homogenous group of patients (treated only with platinum compounds and vinorelbine first-line chemotherapy) and large number of analysed polymorphisms (14 SNPs located in 9 genes). However, in order to verify the obtained results large prospective study should be carried out.

Conclusions

As shown, several SNPs of genes, whose proteins are involved in the mechanism of action of currently used cytostatics may play important role in predicting the adverse events of platinum compounds and vinorelbine chemotherapy in NSCLC patients. Probably, different types of chemotherapy toxicities are depend on SNPs in *XPX*, *XPD*, *XRCC1* and *STMN1* genes. Determination of selected SNPs of genes encoding DNA repair enzymes and protein associated with regulation of cell division may become a useful tool for predicting the toxicity associated with chemotherapy in NSCLC patients.

Compliance with Ethical Standards

Conflict of interest The authors declare no conflicts of interest regarding this study.

Informed consent "Informed consent was obtained from all individual participants included in the study".

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